REMARKS

Claims 2 to 17 and 56 to 59 were pending in the present application, claims 1 and 18-55 having been previously canceled. By virtue of this response, claim 59 has been canceled, and claims 2, 3, 4, 5, 6, 7, 8, and 56 have been amended. Accordingly, claims 2 to 17 and 56 to 58 are currently under consideration. Applicant respectfully requests allowance of the pending claims as amended.

With respect to all claim amendments and cancellations, Applicant has not dedicated or abandoned any unclaimed subject matter. Applicant reserves the right to prosecute any presently unclaimed embodiments in future continuation and/or divisional patent applications.

Claim amendments

Claims 2, 3, 4, 5, 6, 7, 8, and 56 have been amended and claim 59 has been canceled by virtue of this amendment.

Claim 2 has been amended to recite "a second quantitative lipid metabolite profile *from a second biological sample that is different from the first biological sample*." Support for that amendment can be found throughout the specification, *e.g.*, on p. 37, lines 16 to 19; p. 12, line 17, to p. 13, line 23; p. 9, lines 8 to 11; and p. 10, lines 16 to 19.

Claims 3, 4, 5, 6, 7, 8, and 56 have been amended to make their language consistent with the language of amended claim 2.

Accordingly, the amendments are fully supported and no new matter is added.

Prior rejections

Applicant thanks the Examiner for withdrawing the following rejections in view of amendments and arguments in the Response filed December 19, 2007:

(1) claims 2, 3, 5, 6, 12, and 56 to 58 under 35 U.S.C. § 102(b) as allegedly anticipated by Ruan et al. (*J. Dairy Sci.* 81:9-15 (1998))("Ruan");

(2) claims 15 and 16 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan, further in view of Moser et al. (*Ann. Neurol.* 45:100-110 (1999))("Moser");

(3) claims 7, 9, and 13 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan, further in view of Watkins et al. (*J. Lipid Res.* 39:1583-1588 (1998))("Watkins");

(4) claims 4 and 14 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan, further in view of Watkins and Siguel (U.S. Patent No. 5,075,101)("Siguel");

(5) claim 10 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan, further in view of Grav et al. (*J. Chromatography* 658:1-10 (1994))("Grav"); and

(6) claim 17 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan, further in view of "The World of Membrane Lipids," [http://www.biochem.Missouri.edu/~lesa/LIPIDS/membrane_lipid.html; accessed on December 6, 2006; page made on February 2, 1999]("The World of Membrane Lipids").

Rejections under 35 U.S.C. § 103(a)

1. Claims 2, 3, 5, 6, 12, and 56 to 59

Claims 2, 3, 5, 6, 12, and 56 to 59 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane et al. (*Electrophoresis*, 18:1796-1806 (1997))("MacFarlane"), as evidenced by the definition of "metabolism" from Webster's Ninth New Collegiate Dictionary ("Webster's") and the definition of "metabolite" from Mosby's Dictionary of Medicine, Nursing, and Health Professions ("Mosby's"). Office Action, p. 4.

The Office alleges that it would have been obvious at the time of the invention for one of ordinary skill in the art "to modify the heat map analysis of lipids in Ruan et al. by use of the electrophoretic analysis in MacFarlane et al. because it is obvious to substitute [one] known element[for another] to yield a predictable result." *Id.* The Office further alleged that the skilled artisan would have had a reasonable expectation of success in substituting the method of

MacFarlane for the MRI method described in Ruan "because the intensity of the peaks in the electropherograms [is] also proportional to concentrations of the lipid species." *Id.*

Applicant respectfully traverses. To establish a *prima facie* case of obviousness for a method claim based on the rationale that it constitutes no more than the simple substitution of one known element for another to obtain predictable results, the Office must show that (1) "the prior art contained a device (method, product, etc.) which differed from the claimed device [method, product, etc.] by the substitution of some components (step[s], element[s], etc.) with other components [(steps, elements, etc.)]"; (2) that the substituted components (steps, elements, etc.) were known in the art; and (3) that one of skill in the art could have substituted one known step for another, and that the results of the substitution would have been predictable. MPEP § 2143, at p. 2100-130. Applicant respectfully asserts that the Office has not established a *prima facie* case of obviousness for claims 2, 3, 5, 6, 12, and 56 to 59 because Ruan does not disclose a method for presenting analysis of quantitative lipid metabolite profiles differing from the claimed method by the substitution of some steps with other steps known in the art, and the substitution of MacFarlane's methods of electrophoretic analysis of lipoproteins for Ruan's water- and oil-suppressed MRI imaging methods does not remedy that defect.

A. The MRI methods of Ruan

Ruan describes a magnetic resonance imaging ("MRI") technique for use in mapping moisture and fat content in a cheese block. To develop that method, Ruan used homogeneous samples consisting of oil-in-water emulsions prepared with various percentages of Crisco vegetable oil mixed with 3 mM $CuSO_4$ and 3% (v/v) Tween 40 detergent. Ruan, p. 10. The Office contends that "vegetable oil (*i.e.*, Crisco) is inherently a metabolite," defined as "[a] substance produced by metabolic action or necessary for a metabolic process. An essential

metabolite is one required for a vital metabolic process,"[1] according to Mosby's. Office Action, p. 5.

The Office then asserts that Figure 5 of Ruan allegedly shows the "lipid metabolite profile" of various oil-in-water emulsions in a water-suppressed MRI image or in a fat-suppressed MRI image, and contends that Ruan "shows analysis of multiple lipid mixtures" by MRI, which are designated and mapped in Figure 5. *Id.*, pp. 5-7. The Office further alleges that Figure 5 of Ruan inherently "illustrates a 'heat map' of the fat contents of a variety of different lipid composition profiles" because it is "a two dimensional map of multiple lipid profiles marked by shades of colors." *Id.*, pp. 6-7. Finally, the Office speculates that, "[i]f water is considered the internal standard in measuring lipid concentration, it is inherent that a sample of Crisco vegetable oil comprises lipids that [are] compared to the standards of 0% lipid content and 100% lipid content in Figure 5 of Ruan et al." *Id.*, p. 7.

The Office acknowledges that Ruan "does not show comparisons of first and second individual lipid profiles," further noting that the claims "do not require each 'lipid metabolite profile' to be taken from different sets of samples." *Id.*, pp. 6-7. Nevertheless, the Office cites MacFarlane for developing "individual lipoprotein profiles using capillary electrophoresis and mass spectrometry." *Id.*, p. 7. The Office contends that MacFarlane "measures individual lipid profiles," and asserts that "the various types of lipoproteins isolated from blood in MacFarlane et al. (*i.e.*, the electropherograms [in] Figures 2-4) serve as the differing lipid metabolite profiles." *Id.*, p. 9. Finally, the Office concludes that:

> [i]n this instance, it would have been obvious to substitute the electrophoretic methods of MacFarlane for the magnetic resonance imaging techniques of Ruan et al. to yield an alternative method of measuring concentration of the lipid. There would have been a reasonable expectation of success in using electrophoresis in place of MRIs because the intensity of the peaks in the electropherograms are also proportional to concentrations of the lipid species.

[1] Applicant notes that the term "metabolite" is defined in the specification at page 8, lines 3-6, and respectfully refers the Office to that definition, in place of the definition from Mosby's Dictionary of Medicine, Nursing, and Health Professions.

Id., p. 10.

B. The rejection of claims 2 and 5

Applicant respectfully traverses. With respect to the rejection of claims 2 and 5, Applicant notes that the Office correctly observes that Ruan "does not show comparisons of first and second individual lipid profiles." *Id.*, p. 7. In fact, Ruan does not show "individual lipid profiles" at all, but only measures the total fat content (and thus, the total water content) of *the same lipid mixture* at different concentrations (*i.e.*, different concentrations of Crisco vegetable oil in 3 mM $CuSO_4$ and 3% (v/v) Tween 40). As stated in the Office Action dated June 19, 2007, vegetable oils comprise a complex mixture of many different lipids (*i.e.*, triglycerides and the like), each containing a variety of different fatty acids. Office Action of June 19, 2007, p. 7. Thus, Ruan simply measures the total amount of vegetable oil and water present in each sample and displays them side by side. In contrast, the claimed method of presenting analysis of quantitative lipid metabolite profiles comprises the steps of: (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map.

Furthermore, Ruan does not teach the display of a *single* difference or similarity in an individual lipid metabolite between the first and second quantitative lipid metabolite profiles on a heat map, let alone the display of differences or similarities in *a plurality* of individual lipid metabolites between the first and second quantitative lipid metabolite profiles. Even if Crisco vegetable oil were inherently a metabolite and Figures 5A and 5B of Ruan each represented a lipid metabolite profile as the Office suggests (Office Action, pp. 5-6), Ruan would still fail to teach or suggest the display of any differences or similarities in the vegetable oil concentration of Figure 5A compared to the vegetable oil concentration of Figure 5B in a heat map because those Figures simply present analysis of *the same oil-in-water emulsions* by two different imaging methods, the first (Figure 5A) showing oil concentrations by water-suppressed MRI, and the

second (Figure 5B) showing water concentrations by oil-suppressed MRI. In contrast, the claimed method identifies and displays differences or similarities in a plurality of individual lipid metabolites between first and second quantitative lipid metabolite profiles, where the first and second quantitative lipid metabolite profiles are obtained from different biological samples.

The teachings of MacFarlane do not remedy the defects of Ruan with respect to the rejection of claims 2 and 5. The Office correctly observed that MacFarlane presents "individual lipoprotein profiles using capillary electrophoresis and mass spectrometry." Office Action, p. 7. The Office further alleged that "the various types of lipoproteins isolated from blood in MacFarlane et al. (*i.e.*, the electropherograms [in] Figures 2-4) serve as the differing lipid metabolite profiles." *Id.*, p. 9. However, the "individual lipoprotein profiles" of MacFarlane cannot "serve as the differing [quantitative] lipid metabolite profiles" required by the claims because, as the specification makes clear, a "metabolite" is "[a] biomolecule that has a functional and/or compositional role (such as a component of a membrane) in a biological system, and *which is not a molecule of DNA, RNA, or protein.* Examples of metabolites include lipids, carbohydrates, vitamins, co-factors, pigments, and so forth." Specification, p. 8, lines 3-6 (emphasis added).

Furthermore, MacFarlane teaches that "a more effective [cardiac risk profile] might be based *on apoprotein levels rather than the lipid composition of the lipoproteins.*" MacFarlane, p. 1796 (emphasis added). MacFarlane therefore describes methods of preparing "a lipoprotein profile," not a lipid metabolite profile. Those methods comprise (1) separating lipoproteins from serum samples by ultracentrifugation; (2) delipidation of lipoprotein particles; and (3) analysis of the resulting delipidated apoproteins by capillary electrophoresis and electrospray ionization mass spectrometry. *See, e.g.*, MacFarlane, Section 2 (Materials and Methods), pp. 1797-1799. Thus, the electrophoretic methods of MacFarlane were used to analyze individual lipoproteins, not individual lipids. Moreover, the methods of MacFarlane could not be measuring lipid concentrations because lipids were removed from those samples before analysis (*see, e.g.*, MacFarlane, Section 2.4 "Delipidation of lipoprotein particles," p. 1798). MacFarlane therefore does not teach electrophoretic methods for the measurement of individual lipid profiles. On the

contrary, as noted above, MacFarlane suggests that analysis of apoprotein or lipoprotein concentrations may provide a more accurate assessment of an individual's cardiac risk profile then analysis of individual lipid concentrations, thereby teaching away from analysis of lipid metabolite profiles to assess cardiac risk.

Applicant respectfully asserts that the combination of Ruan in view of MacFarlane, as evidenced by the definition of "metabolism" from Webster's and the definition of "metabolite" from Mosby's does not render claims 2 and 5 obvious, because Ruan does not disclose a method for presenting analysis of quantitative lipid metabolite profiles differing from the claimed method by the substitution of some steps with other steps known in the art, and the substitution of MacFarlane's methods of electrophoretic analysis of lipoproteins for Ruan's water- and oil-suppressed MRI imaging methods does not remedy that defect. Therefore, the Office has not established a *prima facie* case of obviousness.

C. The rejection of claims 3, 6 and 12

With respect to the rejection of claims 3, 6, and 12 under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane, as evidenced by the definition of "metabolism" from Webster's and the definition of "metabolite" from Mosby's, the Office first speculates that "[i]f water is considered the internal standard in measuring lipid concentration, it is inherent that a sample of Crisco vegetable oil comprises lipids that [are] compared to the standards of 0% lipid content and 100% lipid content in Figure 5 of Ruan[.]" Office Action, p. 7. The Office later asserts that "water is the standard against which the lipid classes are measured." Office Action, p. 9.

Applicant respectfully traverses. Notwithstanding the Office's allegations, Ruan does not teach use of an internal standard, whether water or any other compound. An internal standard in analytical chemistry is a chemical substance added in a constant amount to samples, the blank, and any calibration standards used in a chemical analysis. The internal standard is then used for calibration by plotting the ratio of analyte signal (*i.e.*, the concentration of individual lipid metabolites) to the internal standard signal (*i.e.*, the concentration of the internal standard) as a

function of analyte concentration of the calibration standards. Calibration to the internal standard signal is done to correct for any loss of analyte during sample preparation or analysis. Thus, an internal standard is typically a compound that closely matches the physical and chemical characteristics of the chemical species being analyzed, so that the effects of sample preparation should, relative to the amount of each species, be the same for signal from the internal standard as for signal from the species being analyzed. For example, the specification teaches that

> [i]n general, the internal standards are compounds that share a lipid class with the target metabolites (i.e. an internal standard for triacylglyceride metabolites is itself a triacylglyceride), but have fatty acids as constituents that are not present in the sample being analyzed. An internal standard for any given lipid class is selected to behave sufficiently similarly to the target metabolites such that there is essentially no discrimination (selective loss or retention) of the internal standard relative to the target metabolites at any step of the analytical process before the analysis.

Specification, p. 27, lines 29-35. Thus, one skilled in the art would recognize that the water in an oil-in-water emulsion is not an internal standard for analysis of individual lipid concentrations in a complex mixture such as vegetable oil, because it is not a compound "that share[s] a lipid class with the target metabolites[.]"

The teachings of MacFarlane do not remedy the defects of Ruan with respect to the rejection of claims 3, 6, and 12. The Office alleges that MacFarlane teaches use of "internal standards of electroosmotic flow markers as markers to calibrate a lipid sample with electroosmotic flow in the capillary." Office Action, p. 12. However, the "internal standard" of MacFarlane is simply "a 1 second duration pressure pulse of H_2O which served as the EOF marker," *i.e.*, to verify that the samples were moving along the capillary gel, rather than an internal calibration standard used to correct for any loss of analyte (*e.g.*, the delipidated apolipoprotein being analyzed). MacFarlane, p. 1798.

Applicant respectfully asserts that the combination of Ruan in view of MacFarlane, as evidenced by the definition of "metabolism" from Webster's and the definition of "metabolite"

from Mosby's does not render claims 3, 6 and 12 obvious, because Ruan does not disclose a method for presenting analysis of quantitative lipid metabolite profiles differing from the claimed method by the substitution of some steps with other steps known in the art, and the substitution of MacFarlane's electroosmotic flow markers for Ruan's alleged use of water as an internal standard in its MRI methods does not remedy that defect. Therefore, the Office has not established a *prima facie* case of obviousness.

D. The rejection of claims 56 to 59

With respect to the rejection of claims 56 to 59, the Office alleges that Figure 5 of Ruan shows an increase or decrease in an individual metabolite by color, and that the amount of increase or decrease in concentration is indicated by the intensity of the color (claim 56), that the figures, tables, and equations of Ruan serve as written reports (claim 57), and that Figure 5 of Ruan shows "the control lipomic profiles at the 100% and 0% levels for lipid and for water (claim 58). The Office further asserts that "[a]bsent a definition of 'control lipomic profile' in the specification, the lipomic profile in Ruan et al. is interpreted to be a control lipomic profile." Office Action, p. 12. Applicant has canceled claim 59, rendering that aspect of the rejection moot.

Applicant respectfully traverses. Claims 56 to 58 all depend from claim 2, and therefore incorporate by reference all the elements of that claim. As discussed above, Ruan does not teach analysis of individual lipid metabolites, or a method comprising a step of "identifying differences or similarities in *a plurality of individual lipid metabolites* between the first and second quantitative lipid metabolite profiles," but only measures the **total fat** content (and thus, the total water content) of the same lipid mixture at different concentrations (*i.e.*, different concentrations of Crisco vegetable oil in 3 mM $CuSO_4$ and 3% (v/v) Tween 40). Thus, Applicant respectfully asserts that Figure 5 of Ruan does not show "an increase or decrease in *an individual* metabolite by color," and does not indicate "the amount of increase or decrease in concentration . . . by the intensity of the color" as required by claim 56 (emphasis added). Nor do the "figures, tables, and equations" of Ruan comprise a written report presenting the results of such analysis, as required by claim 57.

With respect to the rejection of claim 58, as discussed above, Figure 5 of Ruan presents analysis of *the same oil-in-water emulsions* by two different imaging methods (*i.e.*, water-suppressed MRI and oil-suppressed MRI), and does not identify differences or similarities between a plurality of individual lipid metabolites in two different quantitative lipid metabolite profiles, one of which is a control sample, as required by claim 58. Furthermore, Applicant respectfully refers the Office to the specification, which discloses that a control lipomic profile may be, for example, "a compiled lipomic profile assembled from a plurality of individual lipomic profiles, or a pre-condition (*e.g.*, pre-treatment) lipomic profile" from a subject. Specification, p. 13, lines 1 to 3. The data presented in Ruan are neither.

The teachings of MacFarlane do not remedy the defects of Ruan with respect to the rejection of claims 56 to 58. As discussed above, MacFarlane discloses "individual lipoprotein profiles using capillary electrophoresis and mass spectrometry." Office Action, p. 7. However, the "individual lipoprotein profiles" of MacFarlane cannot be the "quantitative lipid metabolite profiles" required by the claims because, as the specification makes clear, a "metabolite" is "[a] biomolecule that has a functional and/or compositional role (such as a component of a membrane) in a biological system, and *which is not a molecule of DNA, RNA, or protein.* Examples of metabolites include lipids, carbohydrates, vitamins, co-factors, pigments, and so forth." Specification, p. 8, lines 3-6 (emphasis added).

Applicant respectfully asserts that the combination of Ruan in view of MacFarlane, as evidenced by the definition of "metabolism" from Webster's and the definition of "metabolite" from Mosby's does not render claims 56 to 58 obvious, because Ruan does not disclose a method for presenting analysis of quantitative lipid metabolite profiles differing from the claimed method by the substitution of some steps with other steps known in the art, and the substitution of MacFarlane's methods of generating lipoprotein profiles by capillary electrophoresis for Ruan's MRI methods of measuring the total fat content of oil-in-water emulsions does not remedy that defect. Therefore, the Office has not established a *prima facie* case of obviousness.

Thus, for the reasons set forth above, Applicant respectfully asserts that the combination of Ruan and MacFarlane, as evidenced by the definition of "metabolism" from Webster's and the definition "metabolite" from Mosby's, does not render the claimed invention obvious. Applicant therefore respectfully asks that the rejection of claims 2, 3, 5, 6, 12, and 56 to 59 under 35 U.S.C. § 103(a) be withdrawn.

2. Claims 15 and 16

Claims 15 and 16 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's, further in view of Moser. The Office alleges that Ruan and MacFarlane "make obvious a comparative profile of lipid concentrations," but acknowledged that neither Ruan nor MacFarlane teach chromatography. Office Action, p. 13. The Office cited Moser as allegedly teaching quantitation of various very long chain fatty acids by a two-column capillary gas liquid chromatographic method, and alleged that:

> [i]t would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the lipid composition studies of Ruan and MacFarlane by use of the chromatographic analysis of Moser et al., wherein the motivation [to combine the references] would have been that while the aforementioned studies quantify lipids, Moser has the advantage of using chromatographic analysis of lipids to specifically address peroxisomal disorders[.]

Office Action, pp. 13-14.

Applicant respectfully traverses. The combination of Ruan and MacFarlane as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, as evidenced by the definitions of "metabolism" from Webster's and the definition "metabolite" from Mosby's, further in view of Moser, cannot render claims 15 and 16 obvious.

Claims 15 and 16 depend indirectly from claim 2, and therefore incorporate by reference all the elements of that claim. As discussed above, the combination of Ruan and MacFarlane

does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of Moser regarding chromatography do not remedy the deficiencies of Ruan and MacFarlane. Applicant therefore respectfully asks that the rejection of claims 15 and 16 under 35 U.S.C. § 103(a) be withdrawn.

3. Claims 7, 9, and 13

Claims 7, 9, and 13 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, further in view of Watkins. The Office again alleges that Ruan and MacFarlane "make obvious a comparative profile of lipid concentrations," but acknowledged that neither reference teaches "use of cardiolipins and specifically the linoleic acid 18:2n6." Office Action, at pp. 14-15. The Office cited Watkins as allegedly teaching quantification of cardiolipins in mitochondria, and alleged that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid composition study of Ruan et al. and MacFarlane et al. by use of the cardiolipin study of Watkins et al., wherein the motivation [to combine the references] would have been that while Ruan et al. and MacFarlane et al. quantify lipids, Watkins et al. has the advantage of quantifying cardiolipins in mitochondria for the purpose of understanding oxidant production and aging[.]

Id., p. 15.

Applicant respectfully traverses. The combination of Ruan and MacFarlane as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, as evidenced by the definitions of "metabolism" from

Webster's and the definition "metabolite" from Mosby's, further in view of Watkins, cannot render claims 7, 9, and 13 obvious.

Claims 7, 9, and 13 depend indirectly from claim 2, and therefore incorporate by reference all the elements of that claim. As discussed above, the combination of Ruan and MacFarlane does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of Watkins regarding cardiolipins do not remedy the deficiencies of Ruan and MacFarlane. Applicant therefore respectfully asks that the rejection of claims 7, 9 and 13 under 35 U.S.C. § 103(a) be withdrawn.

4. Claims 4 and 14

Claims 4 and 14 stand rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane and Watkins, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 7, 12, 13, and 56 to 59 above, and further in view of Siguel. The Office alleges that Ruan, MacFarlane, and Watkins "make obvious the method of fatty acid analysis," but acknowledged that neither reference teaches "the specific molecules of the claims, including the above mentioned 5, 8, 11-eicosatrienoic acid (Mead acid)." Office Action, p. 16. The Office cited Siguel as allegedly teaching that:

> [m]ead acid is an essential fatty acid important in preventing essential fatty acid deficiency," and concluded that "[i]t would have been obvious for someone of ordinary skill in the art at the time of the instant invention to modify the lipid mixture analyses of Ruan et al., MacFarlane et al., and Watkins et al. by the use of Mead acid in Siguel, wherein the motivation [to combine the references] would have been that Siguel shows the advantage of Mead Acid in that adequate amounts of Mead acid are required to prevent lipid deficiency in the blood[.]

Id.

Applicant respectfully traverses. The combination of Ruan in view of MacFarlane and Watkins, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 7, 12, 13, and 56 to 59 above, and further in view of Siguel, cannot render claims 4 and 14 obvious.

Claims 4 and 14 depend indirectly from claim 2, and therefore incorporate by reference all the elements of that claim. As discussed above, the combination of Ruan, MacFarlane and Watkins does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of Siguel regarding mead aciddo not remedy the deficiencies of Ruan, MacFarlane, and Watkins. Applicant therefore respectfully asks that the rejection of claims 4 and 14 under 35 U.S.C. § 103(a) be withdrawn.

5. Claim 8

Claim 8 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, further in view of Dutta et al. (*J. Am. Oil Chem. Soc.* 74(6):647-657 (1997))("Dutta"). The Office alleges that Ruan and MacFarlane "make obvious a comparative profile of lipid concentrations," but acknowledged that neither reference teaches use of cholestan-3b-ols. Office Action, p. 17. The Office cited Dutta as allegedly teaching synthesis and study of oxidation products of sitosterol and campesterol, including 2,4-alpha-methyl-5-cholestan-3b-ol, and concluded that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Ruan et al. and

> MacFarlane et al. by use of the phytosterol quantitation method of Dutta et al., wherein the motivation [to combine the references] would have been that the study of Dutta et al. has the advantage of using the required fatty acids for further understanding of [the] biological implications of cholesterols and phytosterols[.]

Id.

Applicant respectfully traverses. The combination of Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, further in view of Dutta, cannot render claim 8 obvious.

Claim 8 depends indirectly from claim 2, and therefore incorporates by reference all the elements of that claim. As discussed above, the combination of Ruan and MacFarlane does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of Dutta regarding oxidation products of sitosterol and campesterol do not remedy the deficiencies of Ruan and MacFarlane. Applicant therefore respectfully asks that the rejection of claim 8 under 35 U.S.C. § 103(a) be withdrawn.

6. Claim 10

Claim 10 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, further in view of Grav. The Office alleges that Ruan and MacFarlane "make obvious a comparative profile of lipid concentrations," but acknowledged that neither reference teaches "specific

internal standards to be used." Office Action, pp. 18-19. The Office cited Grav as allegedly teaching use of diheptadecanoyl phosphatidylcholine as an internal standard, and concluded that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Ruan et al. and MacFarlane et al. by use of the . . . specific standards of Grav et al., wherein the motivation would have been that while Grav et al. disclose a method of quantifying lipids in livers, Grav et al has the advantage of using the required internal standards in a direct health application in examining hypolipemia and hyperlipemia[.]

Id.

Applicant respectfully traverses. The combination of Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59 above, further in view of Grav, cannot render claim 10 obvious.

Claim 10 depends indirectly from claim 2, and therefore incorporates by reference all the elements of that claim. As discussed above, the combination of Ruan and MacFarlane does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of Grav regarding the use of diheptadecanoyl phosphatidylcholine as an internal standard do not remedy the deficiencies of Ruan and MacFarlane. Applicant therefore respectfully asks that the rejection of claim 10 under 35 U.S.C. § 103(a) be withdrawn.

7. Claim 17

Claim 17 stands rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and

"metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59, and further in view of "The World of Membrane Lipids." The Office alleges that Ruan and MacFarlane "make obvious a comparative profile of lipid concentrations," but acknowledged that neither reference teaches "the use of a web page for electronically display[] of results." Office Action, p. 20. The Office cited "The World of Membrane Lipids" as allegedly teaching use of a website for display of "membrane lipid crystal structures . . . [and] information about the nomenclature, crystallization, etc. of membrane lipids," and concluded that:

> [i]t would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the lipid quantification method of Ruan et al. and MacFarlane et al. by use of the web posting database of "The World of Membrane Lipids," wherein the motivation would have been that posting lipid results on a web page has the advantage of making the data available to the general public[.]"

Id., p. 21.

Applicant respectfully traverses. The combination of Ruan in view of MacFarlane, as evidenced by the definitions of "metabolism" from Webster's and "metabolite" from Mosby's as applied to claims 2, 3, 5, 6, 12, and 56 to 59, and further in view of "The World of Membrane Lipids," cannot render claim 17 obvious.

Claim 10 depends directly from claim 2, and therefore incorporates by reference all the elements of that claim. As discussed above, the combination of Ruan and MacFarlane does not teach a method for presenting analysis of quantitative lipid metabolite profiles comprising (1) designating a first quantitative lipid metabolite profile from a first biological sample and a second quantitative lipid metabolite profile from a second biological sample that is different from the first biological sample; (2) identifying differences or similarities in a plurality of individual lipid metabolites between the first and second quantitative lipid metabolite profiles; and (3) displaying the identified differences or similarities on a heat map, and the teachings of "The World of Membrane Lipids" regarding the use of a website to display information about lipids do not remedy the deficiencies of Ruan and MacFarlane. Applicant therefore respectfully asks that the rejection of claim 17 under 35 U.S.C. § 103(a) be withdrawn.

CONCLUSION

Applicant respectfully asserts that the pending claims are in condition for allowance in view of the remarks and amendments above. Accordingly, Applicant respectfully asks the Office to withdraw the outstanding rejections of the claims and to pass this application to issue. If the Office believes that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, Applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to ***Deposit Account No. 03-1952*** referencing **Docket No. 475512000100**. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: August 25, 2008

Respectfully submitted,

Electronic signature: /David C. Hoffman/
David C. Hoffman
Registration No.: 59,821

MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-4019